that this sentence should be ignored, and should not have been included in the Office Action.

A second question was raised regarding the last paragraph of Section III on p. 9 of the Office Action, which states that "recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense" because Applicants were not sure what these sentences meant. Examiner Cook asserted that the Applicants need to explain why the prior art does not have the limitations of the currently pending claims relative to the antibodies, so these sentences mean the pending claims have a language problem and it is necessary to distinguish the pending claims from the prior art.

Summary of the Telephone Interview of October 8, 2003

Examiners Cook and Le were present, as were attorneys Bruce D. Sunstein and Barbara J. Carter. The term "substantially all" was discussed, in the context of the pending rejection under 35 U.S.C. § 112, para. 2 (indefiniteness) of claim 1 (see Office Action, p. 3, para. 3. A.). Attorneys for the Applicants submitted that the term "substantially all" is a term of art, readily understood by those of skill in the art, and not "a relative term" as stated in the Office Action (id.) because the Griffin reference, the keystone patent in preparing aptamers of desired binding affinity, fully explores the binding affinities required to design any aptamer of any desired specificity and is referenced in the application and well-known to those skilled in the art. Other arguments were presented, and Examiners Cook and Le stated that all would be considered in the response. No agreement on this issue was reached.

The reference of Jayasena et al. (US5,989,823) in the context of an obviousness rejection under 35 U.S.C. § 103(a) was also discussed. Attorneys Sunstein and Carter explained Fig. 2 of Jayasena et al, and pointed out that the fluorescence quantification/detection system, which requires a second nucleic acid ligand (a ligand beacon) is entirely different, and not compatible with, the presently claimed invention. First, as stated in the previous response of July 11, 2003 (Response D), Jayasena et al. required two nucleic acid ligands for quantification and the presently claimed invention requires only one. More importantly, the presently claimed invention requires use of a

"quantitative replicative procedure" (see Application, claim 1(d)). In contrast, Jayasena. et al. uses a fluorescently tagged ligand beacon for quantification, by quenching of the fluorescent signal when the aptamer ligand binds to the target sequence and does not use a quantitative replicative procedure. Examiners Cook and Le understood the distinction, and agreed to consider this argument in Applicants' response. No agreement on this issue was reached.

The claimed subject matter is allowable over the art of record.

As stated in the previous response of July 11, 2003 (Response D), and discussed in the telephone interview of October 8, 2003, the rejections, for obviousness, depend on combinations of Griffin with Jayasena et al. in view of various other references. Griffin does not each the invention claimed herein because Griffin stops where the presently claimed invention starts. Griffin is important only as background art for someone of skill in the art because it teaches how to design aptamers of any required specificity using binding affinity as the major screening criterion (see Griffin, generally). In contrast, claim 1 of the present application is a "method for quantitatively assaying one or more target molecules in a first sample, comprising: adding to the first sample, *a preparation of nucleic acid aptamer specific for each target molecule*;" (see claim 1, emphasis added). In claim 1, the specific aptamers have been designed, selected, obtained – outside the scope of the claim – independently of the claimed subject matter. The only connection Griffin has to the presently claimed invention is that the SELEX method of Griffin has been cited as one way to obtain aptamers specific for the target molecules of interest. It is like citing the original PCR reference for how one might use PCR in a particular method. Griffin is the seminal reference for the SELEX method, and so is important as a reference for preparation of aptamers with specificity to a target molecule, but is not relevant as a § 103 (a) reference against the presently claimed invention which does not claim preparation of aptamers with specificity, but rather claims a "method for quantitatively assaying one or more target molecules in a first sample," wherein the method requires use of a "quantitative replicative procedure" – i.e., QPCR, for example.

The office action maintains that Jayasena et al. "teach methods involving the quantification (measurement of concentration) of a target in a test mixture", using aptamers. Office action, p. 5. But as argued in Response D, and re-stated during the

telephone interview of October 8, 2003, the presently claimed invention requires "using a quantitative replicative procedure to determine a quantity of aptamer specific for each target molecule". A quantitative replicative procedure, as required by the claims, may be implemented by using a quantitative polymerase chain reaction. Application, for example, at p. 5, lines 22-23. Jayasena's procedure for quantification is nothing of this kind—it does not use a quantitative replicative procedure— but instead requires "simply comparing the fluorescence measurement with that obtained from a control." Col. 5, lines 36-40. Further, Jayasena et al. utilize a second nucleic acid ligand, a ligand beacon, that contains a fluorescent tag. As seen in Figure 2 (Jayasena et al.), the ligand beacon binds to the aptamer and fluoresces. Upon binding of the aptamer to the target sequence, thus displacing the ligand beacon, fluorescence is quenched. It is the quenching of fluorescence that is measured and used to infer quantification of the amount of aptamer bound to the target sequence. This method is completely incompatible with the presently claimed invention, which measures the amount of bound aptamer using a quantitative replicative procedure, and teaches away from the claimed invention. One skilled in the art would not be motivated to combine the teachings of Jayasena et al., which discloses an incompatible quantification system requiring a ligand beacon having a hairpin structure when not bound (and thus does not fluoresce when unbound) with Griffin, which merely shows how the SELEX method allows design and selection of aptamers having any desired specificity to a target sequence, but discloses nothing about quantification of a target sequence. Neither reference, whether alone or in combination, teaches the claimed invention, nor suggests modifying the disclosed methodologies to arrive at the claimed invention, nor suggests combining these references to arrive at the claimed invention.

As stated in Response D filed July 11, 2003, and herein reiterated, Jaysena et al. teach that quantification of target-specific aptamer that is bound to the target should be accomplished by measuring a binding phenomenon that is wholly distinct from the aptamer-target combination—namely the aptamer-ligand beacon combination that produces the fluorescence.

Of course, the quantitative replicative procedure required by the claims herein looks directly at the aptamer that *is* bound to the target, and not (as Jayasena does) to

unbound aptamer. Indeed, claim 1 requires, in element (c), separating the unbound aptamer, and the quantitative replicative procedure of element (d) is used on the second sample containing bound aptamer only when the unbound aptamer has been separated.

In sum, Jayasena uses an approach that is completely different from that which is claimed herein. Not only is there no disclosure in Jayasena of the subject matter herein, but also the reference teaches away from the subject matter claimed herein.

As a final note, the Office Action states on p. 9 that "It has been held that the recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense." (Cited to *In re Hutchinson*, 69 USPQ 138). These are the two sentences that were discussed in the telephone conference of October 1, 2003, wherein the Examiner stated that there is a language problem that needs to be addressed. First, in re Hutchinson deals with *claim limitations*, not language in the specification generally. (see In re Hutchinson, the final paragraph that spans the bottom of p. 140, col. 2, and ends on the top of p. 141, col. 1). In the present case, the language "is capable of" does not appear in the claims as a limitation; in fact, it does not appear in the claims at all. This language appears in the specification five times – three times on p. 2, at lines 6, 16 and 18, each dealing with a discussion of the Griffin et al. SELEX reference (using language taken directly from Griffin et al. – see e.g. col. 10, lines 35-39); once on p. 13, line 7 in connection to the quantitative replicative procedure being "capable of amplifying a single nucleic acid, in theory"; and once on p. 20, line 7 where it states: "Recent re-exposure to rubella would enable that person to expand the number of clones of B cells and the number of each clone capable of synthesizing the IgG molecules that can bind the F_{AB} sites to the antigens on the virus." None of these references relate to claim limitations. Therefore, Applicants fail to see how there is a language problem.

Further, In re Hutchinson never states that the language "capable of" does not constitute a limitation in any patentable sense. What *In re Hutchinson* actually says is – "Taking the first claim 42 ... the introductory clause to the effect that the laminated article is "*adapted*" for use in making a template .... does not constitute a limitation in any patentable sense..." *See id.*, col. 2, section [4]. Further, *In re Hutchinson* deals with article claims, not method claims, ("Each of them [the claims under appeal] contains

functional statements which may not be regarded as limiting the claims, they being article claims.") as is the case with the present application. For these reasons, Applicants respectfully submit that *In re Hutchinson* is not relevant to the present case.

Given that the rest of the § 103 (a) rejections hinge on the combination of Griffin with Jayasena et al., Applicants respectfully submit that all pending claims meet the requirements of 35 U.S.C. § 103(a).

The application meets the requirements of § 112.

The office action maintains that the term "substantially all" is a relative term which renders claim 1 indefinite (see Office Action, p. 3). As argued in Response D filed July 11, 2003 and again in the telephone interview of October 8, 2003, and as stated above, Applicants respectfully submit that "substantially all" is a term of art, readily understood by those of skill in the art, and not "a relative term" as stated in the Office Action (*id.*). As previously discussed, the Griffin reference, the keystone patent in preparing aptamers of desired binding affinity, fully explores the binding affinities required to design an aptamer of any desired specificity and is referenced in the application and well-known to those skilled in the art.

To reiterate those arguments: A person of ordinary skill in the art is one who would understand and have access to the concepts that are set forth in the art cited by the Examiner in rejecting the claims—particularly Griffin and Jayesena—and which is undisputedly enabling for the subject matter disclosed, given that these references were asserted as a basis for rejection under 35 U.S.C. § 103. *Seymour v. Osbourn*, 78 U.S. 516, 555 (1870); *Preemption devices, Inc. v. Minnesota Mining and Manufacturing Co.*, 732 F.2d 903, 906 (Fed. Cir. 1984). Griffin and Jayesena both specifically describe the SELEX process in detail, which enables the selection of a high-affinity aptamer for a specified target. E.g. Jayesena, col. 11, line 50 through col. 13, line 45. See additionally PCT WO 99-07724 referred to in the application on p. 2, lines 3-8, and incorporated by reference therein, reference AE as submitted herein, p. 1, line 31 to p. 5, line 28. Binding phenomena are, and are well known in the art to be, equilibrium processes. The power of the SELEX method is the ability to select and enrich for aptamers to a desired target that

have unprecedented specificity and therefore high-affinity binding to the desired target. *Id.*

In the present case, the claim defines an assay and the assay quality is dependent on aptamer design. A person of ordinary skill in the art knows, by reading claim 1 and the application, that the aptamer that is bound to the target is what is measured using a quantitative replicative procedure. The measurement of bound aptamer thus determines the measurement of the target molecule so aptamer design affects the quality of measurement. Aptamer design, in turn, is taught in the application by reference to Griffin et al and other references (see above). Therefore the application teaches that the assay can be designed with any desired accuracy and precision. The accuracy and precision depend on the aptamer binding affinity, which can be made as high as is desired. The extent of reaction with aptamer in element (b) of claim 1 depends on binding affinity of the aptamer with its target. Thus, "substantially all" is interpreted in relation to the desired binding affinity and corresponding the accuracy and precision.

It is therefore certain that a person of ordinary skill in the field of the subject matter claimed herein can implement the target-specific aptamer selection and subsequent enrichment to provide high affinity aptamer with any desired low Kd binding affinity to provide any desired level of discrimination. This is the context in which "substantially all" is readily understood by a person of ordinary skill in the art.

In other words, when one looks to the application in view of the prior art of record, the context is perfectly clear to a person of ordinary skill in the art what is meant here by "substantially all".

Conclusion

It is believed that no extension of time is needed; however, this conditional petition for an extension of time is being made in the event that the need for an extension has been overlooked. Further, if any additional fees are required for the timely consideration of this application, please charge deposit account number 19-4972.

It is submitted that all of the claim rejections have been addressed and that all of the pending claims are now in a condition for allowance. Accordingly, Applicants

respectfully request reconsideration of the application and issuance of a notice of allowance. The Examiner is requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

Respectfully submitted,

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